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as the groups of amino acids which in and of themselves are biochemically similar. Applicants draw the Examiner's attention to pages 17-21 of Biochemistry, 3d ed., by Lubert Stryer, 1988 attached hereto as Exhibit B. Each of the twenty amino acids are grouped into families of like amino acids. These families suggest candidates for conservative substitutions, additions and deletions.

Accordingly, applicants respectfully request the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, second paragraph.

In summary, for the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for rejection and objection set forth in the October 31, 1995 Office Action and earnestly solicit allowance of the claims now pending in the subject application, namely claims 1 and 2.

#### INFORMATION DISCLOSURE STATEMENT

Applicants wish to have the Examiner make of record in this application, the references previously disclosed in the related co-pending, co-assigned U.S. Serial No. 806,112, filed December 12, 1991. In accordance with their duty under 37 C.F.R. §1.56, applicants would like to direct the Examiner's attention to the following:

1. U.S. Patent 4,753,894 issued January 28, 1988 to Frankel et al. discloses murine monoclonal antibodies which bind selectively to human breast cancer. Although seven of the antibodies are stated in columns 15-16 to bind to a common monomeric, approximately 210kD protein found in cancerous breast tissue, there is no disclosure that any of the

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antibodies bind to the extracellular domain of the human neu gene encoded protein.

2. U.S. Patent 4,803,169 issued February 7, 1989 to Linsley et al. discloses methods for detecting, staging and monitoring human breast cancer involving determining the amount of two antigens, designated W1 and W9 in serum via quantitative immunoassays. The W1 and W9 antigens are characterized as having a molecular weight of approximately 260-340kD. There is no disclosure of an antibody that binds to the extracellular domain of the human neu gene encoded protein.
3. Johnson et al., U.S. Patent No. 4,855,241, issued August 8, 1989, describe methods of diagnosing neural tumors by detecting Nerve Growth Factor Receptor (NGFR) in serum. The detection of a truncated NGFR in serum is shown. NGFR is a transmembrane growth receptor that is not a tyrosine kinase.
4. U.S. Patent 4,938,948 issued July 3, 1990 to Ring et al: claims hybridomas producing monoclonal antibodies for imaging and diagnosis of human breast tumors. The monoclonal antibody designated 520C9 is disclosed in columns 1 and 19. Although five of the antibodies are stated in column 19 to bind a monomeric, approximately 200kD protein found in cancerous breast tissue, there is no disclosure that any of the antibodies bind to the extracellular domain of the human neu gene encoded protein.
5. U.S. Patent 5,169,774 issued December 8, 1992 to Frankel et al. is a continuation of U.S. Serial No. 842,476 which is a continuation-in-part of U.S. Serial No. 690,750 which issued as U.S. Patent 4,753,894. U.S. Patent 4,753,894 is described above. U.S. Patent 5,169,774 discloses murine monoclonal

antibodies which bind selectively to human breast cancer. Although seven of the antibodies are stated in column 17 to bind to a common monomeric, approximately 210kD protein found in cancerous breast tissue, there is no disclosure that any of the antibodies bind to the extracellular domain of the human neu gene encoded protein.

6. EP-A-O 206065 describes the detection of oncogenes in serum samples from tumor patients. Only data for ras is presented, abl, fes, fos, fms, myb, myc, ras, src, mos, rel, sis, and yes are cited in the examples. Neu is not mentioned.
7. EP-A-O 214520 describes methods of diagnosing a neoplastic condition associated with the presence of an activated oncogene.
8. WO 87/06692 describes a method of inhibiting growth of tumor cells which overexpress a growth factor receptor or growth factor by treatment of cells with antibodies which inhibit the growth factor receptor function.
9. Akiyama et al., Science, 232:1644-1646 (1986), describe raising antibodies against a synthetic peptide corresponding to 14 amino acid residues at the carboxy terminus of the deduced amino acid sequence from the human c-erbB-2 nucleotide sequence. The antibodies were reported to immunoprecipitate a 185,000 dalton glycoprotein from MKN-7 adenocarcinoma cells.
10. Bargmann et al., Cell, 45:649-657 (1986), describe multiple independent activations of the rat neu oncogene by a point mutation altering the transmembrane domain of p185.
11. Bargmann et al., Nature, 319:226-230 (1986), describe results which suggest that the neu oncogene encodes an epidermal growth factor receptor-related protein.

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12. Basu et al., Mol. Cell. Biol., 9:671-677 (1989), report regulation of the tyrosine kinase activity of epidermal growth factor receptor by a truncated receptor of 100 kilodaltons containing the EGF-binding site but not the kinase domain. It was described that structurally related receptor kinases, such as the platelet-derived receptor, were not inhibited by the truncated 100 kDa receptor.
13. Berger et al., Cancer Res., 48:1238-1243 (1988), describe a study which attempts to correlate c-erbB-2 gene amplification and protein expression with lymph node status and nuclear grading as well as with axillary lymph node involvement.
14. Carney et al., AACCC Abstract (1988), describe monoclonal antibodies to the human neu oncogene protein.
15. Coussens et al., Science, 230:1132-1139 (1985), describe the identification and characterization of a potential cell surface receptor of the tyrosine kinase gene family using molecular cloning techniques. The primary sequence was similar to that of the human epidermal growth factor receptor and the v-erbB oncogene product; the chromosomal location of the gene for this protein was coincident with the neu oncogene.
16. Downing et al., Mol. Cell. Biol., 9:2890-2896 (1989), describe the presence of the extracellular domain of CSF-1R in the culture media of CSF-1R expressing cells. CSF-1R (fms) is a transmembrane tyrosine kinase growth factor receptor.
17. Drebin et al., Nature, 312:545-548 (1984), describe the generation of monoclonal antibodies stated to react specifically with cell-surface determinants found on NIH 3T3 cells transformed by transfection with a group of rat neuroblastoma oncogenes (the rat neu oncogene).

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18. Drebin et al., Cell, 41:695-706 (1985), describe what is stated to be the rapid and reversible loss of both cell-surface and total cellular p185 of NIH 3T3 cells transformed with the rat neu oncogene which were exposed to monoclonal antibodies reactive with the rat neu gene product.
19. Drebin et al., Oncogene, 2:273-277 (1988), describe monoclonal antibodies stated to be reactive with distinct domains of the rat neu oncogene-encoded p185 molecule which exert synergistic anti-tumor effects in vivo.
20. Drebin et al., Oncogene, 2:387-394 (1988), describe monoclonal antibodies which bind cell surface domains of the rat neu gene encoded product.
21. Gullick et al., Int. J. Cancer, 40:246-254 (1987), describe using antisera generated against two synthetic peptides from the predicted sequence of the human c-erbB-2 protein and a monoclonal antibody specific for the rat neu protein in an investigation of expression of the c-erbB-2 protein in normal and transformed cells.
22. Hung et al., Proc. Natl. Acad. Sci. USA, 83:261-264 (1986), describe molecular cloning of the rat neu gene.
23. Kraus et al., The EMBO J., 6:605-610 (1987), describe that overexpression of the erbB-2 gene in mammary tumor cell lines is frequent and associated with different genetic abnormalities.
24. McKenzie et al., Oncogene, 4:543-548 (1989), describe the generation and characterization of monoclonal antibodies specific for the human neu oncogene product.
25. McKenzie et al., Abstract presented at 4th Annual Oncogene

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- Meeting, Frederick, Maryland (1988), describe the generation and characterization of monoclonal antibodies which recognize the human neu protein.
26. Schecter et al., Science, 229:976-978 (1985), describe that the neu oncogene which was identified in ethylnitrosourea-induced rat neuroglioblastomas, had strong homology with the erbB gene that encodes that epidermal growth factor receptor.
  27. Semba et al., Proc. Natl. Acad. Sci. USA, 82:6497-6501 (1985), describe an examination of the details of the relation between the v-erbB gene and the EGF receptor gene and the possible involvement of this gene in human cancer. The c-erbB-1 and c-erbB-2 genes were identified in the human genome.
  28. Slamon et al., Science, 235:177-182 (1987), describe that neu which is amplified relatively frequently in human breast cancer cell lines was amplified 2 to greater than 20 times in 30% of breast tumors. The presence of neu amplification was stated to be significant predictor of both overall survival time and time to relapse.
  29. Studencki et al., DNA, 3:7-15 (1984), describe a study showing that the complexity of a nonadecanucleotide was sufficient to recognize a unique sequence within the human genome.
  30. Tandon et al., J. Clin. Oncol., 7:1120-1128 (1989), describe a method using Western blot analysis stated to quantitate the HER-2/neu protein level in 728 human breast tumor specimens for the potential prognostic significance.
  31. Trimpe et al., Abstract presented at Cold Spring Harbor Laboratory Meeting (1988), describe a flow cytometric analysis of cerbB-2 and ras oncogene products in human breast carcinoma cells.

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32. Van de Vijer et al., Mol. Cell. Biol., 7:2019-2023 (1987), investigated alteration in the structure and expression of oncogenes in human mammary tumors and mammary tumor-derived cell lines. In 16 of 95 human mammary tumor samples amplification of the human neu oncogene was detected in human mammary tumors and was found to be accompanied frequently by amplification of the linked c-erbA oncogene.
33. Varley et al., Oncogene, 1:423-430 (1987), describe that alterations to either the neu or c-myc proto-oncogene in breast carcinomas correlate with poor short-term prognosis.
34. Venter et al., The Lancet, ii:69-72 (1987), describe amplification of the human proto-oncogene c-erbB-2 in 12 of 36 human breast tumors which was stated to be associated with increased levels of expression of the c-erbB-2 protein, measured by immunohistological staining and by Western blotting.
35. Wong et al., Oncogene, 2:67-72 (1987), used an in vivo experimental oral epithelial carcinogenesis system and stated that certain molecular changes, such as expression of a cellular proto-oncogene, c-erbB can be detected in early stages of tumor development.
36. Yamamoto et al., Nature, 319:230-234 (1986), describe similarities between the protein encoded by the human c-erbB-2 gene and epidermal growth factor receptor.

Copies of the disclosed references were submitted in the parent application and therefore, pursuant to 37 C.F.R. §1.98, are not required to be submitted in the subject application. Each of the references listed above are again listed on the accompanying PTO Form 1449 (Exhibit C).

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Applicants maintain that the subject invention is different and patentably distinct over the compositions and methods disclosed in the above-listed references. Accordingly, applicants maintain that none of the above-listed references teach or suggest the inventions claimed in the subject application.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided.

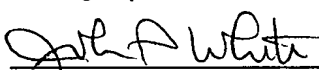
No fee, other than the \$380.00 extension fee and \$220.00 information disclosure fee, is deemed necessary in connection with the filing of this Amendment. However, if any additional fee is required authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this paper is being deposited this date with the U.S. Postal Service as first class mail addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

 4/1/96  
John P. White Date  
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